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Initial topical cooling followed by backtable Celsior flush perfusion provides excellent early graft function in porcine single lung transplantation after 24 hours of cold ischemia

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lung preservation;
low potassium dextran (LPD);
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graft function

BACKGROUND: Topical in situ cooling of the donor lungs is a prerequisite for procurement of non–heart-beating donor lungs and may be of interest for living related lung donation.

METHODS: Twenty-four single lung transplants were performed in 4 groups of Landrace pigs (6 per group). Control LPD, control Celsior and topical cooling in situ, followed by LPD (exLPD) or Celsior (exCel) ex situ flush, were employed. All lungs were perfused antegrade with 1 liter of solution at 4°C. Lungs were stored immersed in preservation solution for 24 hours at 4°C. After transplantation of the left lung, the right recipient bronchus and pulmonary artery were clamped.

RESULTS: Four of 6 animals each in the LPD and Celsior groups and all 6 animals in both the exLPD and the exCel groups survived the 7-hour reperfusion. The mean oxygenation index was favorably preserved in the exCel group at 7 hours after reperfusion (417 ± 81) over all other groups (LPD 341 ± 133, Celsior 387 ± 86, exLPD 327 ± 76; $p < 0.0001$). Pulmonary vascular resistance showed significantly lower values in the Celsior and exCel groups (LPD 1,310 ± 620, Celsior 584 ± 194, exLPD 1,035 ± 361, exCel 650 ± 116 dyn/s/cm^5 at 7 hours after reperfusion; $p < 0.0001$). Consistently, the wet-to-dry lung weight ratio also indicated beneficial graft protection in the exCel group (LPD 8.1 ± 0.8, Celsior 8.4 ± 0.8, exLPD 7.5 ± 1.0, exCel 3.1 ± 0.9; $p < 0.0001$).

CONCLUSION: Initial topical cooling followed by backtable perfusion is a sufficient technique for pulmonary graft preservation providing excellent post-transplant function. Celsior subsequent to in-situ topical cooling revealed the most beneficial results in this setting. This combined technique could advance non–heart-beating, living related lung lobe donation and, potentially, regular heart-beating lung donation.
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More than 40,000 lung transplants have been reported to the registry of the International Society for Heart and Lung Transplantation (ISHLT) since 1989.[1] The demand for lung transplantation continues to increase and a considerable donor organ shortage remains. Lung donor criteria for acceptance have already been extended. Finding alternative sources of organs continues to be a major priority.[1–3]

Use of non–heart-beating organ donors (NHBDs) has been widely investigated, especially with regard to acceptable warm ischemia times, increased periods of in situ topical cooling, and issues of additional flush preservation.[4–9]

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The concept of living related lung lobe donation and transplantation has been described. During graft recovery, the lobar graft may be exposed to warm ischemia in situ. Antegrade, retrograde or no-flush preservation has been employed backtable thereafter.[3,10–14]

Either topical cooling or flush perfusion of the lungs is accepted as safe and sufficient in NHB, living related lobar lung or deceased donor organ donation. Experimental data have revealed beneficial effects combining these approaches.[8,9]

The purpose of this study was to evaluate early graft function after 24 hours of cold ischemic time after topical cooling and subsequent ex situ antegrade flush preservation in comparison to conventional antegrade flush preservation only, aiming toward an effective strategy for living related donation.

Because our own pre-clinical data reflect safe and sufficient graft preservation with Celsior (Cel),[15–18] we evaluated two clinically employed preservation solutions: low-potassium dextran (LPD) solution and Celsior. We hypothesized that initial topical cooling followed by backtable Celsior flush perfusion is a preservation technique that offers good graft function.

Methods

Animal care

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" and the *Guide for the Care of Laboratory Animals*, prepared by the Institute of Laboratory Animal Resources, National Research Council (National Academy Press, revised 1996), as well as ibeing n compliance with the European Convention on Animal Care.

Donor procedure

As preservation solutions, either LPD (Perfadex; Vitrolife, Gothenburg, Sweden) or Celsior (Genzyme Germany, Neu-Isenburg, Germany) were used. LPD was supplemented by 0.3 ml tris hydroxymethyl aminomethane (THAM) buffer/liter. The components of the preservation solutions used are listed in Table 1.

Animals were assigned to 4 groups of 6 animals each. Induction and maintenance of anesthesia was performed as described elsewhere.[15,16,18] The donor animals (weight 27 to 32 kg) were ventilated in a pressure-controlled mode (inspiratory peak pressure 30 cm H_2O, positive end-expiratory pressure [PEEP] 5 cm H_2O, fraction of inspired oxygen [FIO_2] 1.0, inspiration/expiration [I/E] ratio 1:1, ventilation rate 10 breaths/min).

After median sternotomy, the pericardium and both pleural cavities were opened. The heart and lungs were isolated. Then 250 mg of methylprednisolone and 7,500 IU of heparin were administered systemically.

Control groups

For LPD and Celsior controls, a cannula was inserted into the main trunk of the pulmonary artery and secured with a ligature. Simultaneously to cardiac inflow occlusion and drainage of the left heart, the pulmonary artery was clamped centrally of the cannula. Subsequently, in-situ antegrade flush preservation via this cannula was initiated with 1 liter of 4°C cold preservation solution. The perfusion pressure was controlled by a separate catheter and mean pressure was retained at 10 mm Hg by adjusting the static heights in which the containment was hung. Ventilation of the lungs was maintained throughout the entire preservation period. Finally, the trachea was clamped and the heart–lung block was excised.

Table 1 Composition of the Preservation Solutions Used

Component	LPD solution	Celsior
Na^+ (mmol/liter)	138	100
K^+ (mmol/liter)	6	15
Cl^- (mmol/liter)	142	100
Ca^{2+} (mmol/liter)	0	0.25
Mg^{2+} (mmol/liter)	0	13
PO_4^{3-} (mmol/liter)	0.8	0
SO_4^{2-} (mmol/liter)	2	0
Histidine (mmol/liter)	0	30
Mannitol (mmol/liter)	0	60
Dextran-40 (g/liter)	50	0
Glucose (g/liter)	0.91	0
Glutamic acid (mmol/liter)	0	20
Lactobionic acid (mmol/liter)	0	80
Glutathione (mmol/liter)	0	3
Osmolality (mOsm/liter)	292	320
pH	7.4	7.3

Study groups

Fibrillation of the heart was electrically induced, which led to circulatory arrest. Ventilation was stopped simultaneously. The atelectatic lungs were immersed in 3 liters of saline at 4°C within the pleural cavities for 30 minutes. The trachea was clamped and the heart and lungs were then excised en bloc. After separating the heart and lungs the pulmonary artery was clamped. The lungs were antegradely flush preserved with 1 liter of either buffered LPD (exLPD) or Celsior (exCel) ex situ, approximately 3 to 5 minutes after stopping topical cooling.

Although the lungs of the in situ groups were ventilated during the entire flush preservation, ventilation in the ex situ study groups was stopped prior to topical cooling by instillation of cold saline into the pleura.

In all groups, the left lung was separated and the left main bronchus was clamped. Lung grafts of both in situ control groups were stored semi-inflated, in contrast to the lungs of both ex situ study groups, which were stored in an atelectatic state. All lungs were stored for 24 hours at 4°C in the corresponding preservation solution and were then transplanted.

Porcine left-sided lung transplantation

Recipient female pigs (weight 24 to 30 kg) were anesthetized and prepared as described elsewhere.[15,16,18] The intubated animals were ventilated in a pressure-controlled mode (airway peak pressure 30 cm H_2O, PEEP 5 cm H_2O, I/E ratio 1:1, ventilation rate 10 breaths/min) with FIO_2 0.5 throughout the entire observation period.

Recipient systemic arterial and central venous pressures were monitored by catheters inserted into the right carotid artery and jugular vein. Pulmonary artery hemodynamic was assessed via a